Mechanism of hyperglycemia-induced tissue damage

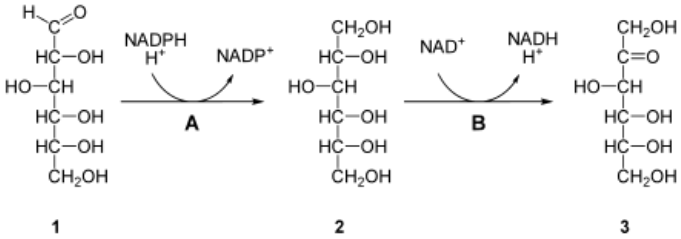
Prolonged hyperglycemia occurs with insulin resistance or diabetes mellitus. It leads to later complications that reduce length and quality of life.

Mechanisms of action of hyperglycemia

Polyol path

Glucose, catalyzed by *aldose reductase*, converts to **sorbitol** (NADPH → $NADP^+$). Increased consumption of reduced coenzymes causes insufficient regeneration of glutathione (decrease of antioxidant protection, increase in oxidative stress).

Sorbitol cannot pass through the plasma membrane. This changes the osmolarity of the cells and causes edema. It can be converted to fructose, with the formation of reduced coenzymes (NAD → NADH).



In physiological situations, the polyol pathway is used to remove toxic aldehydes.

Superoxide formation

Excessive amount of reduced coenzymes (formed during the conversion of sorbitol to fructose) cause a block of complex III in mitochondria. Coenzyme Q remains reduced and superoxide is formed.

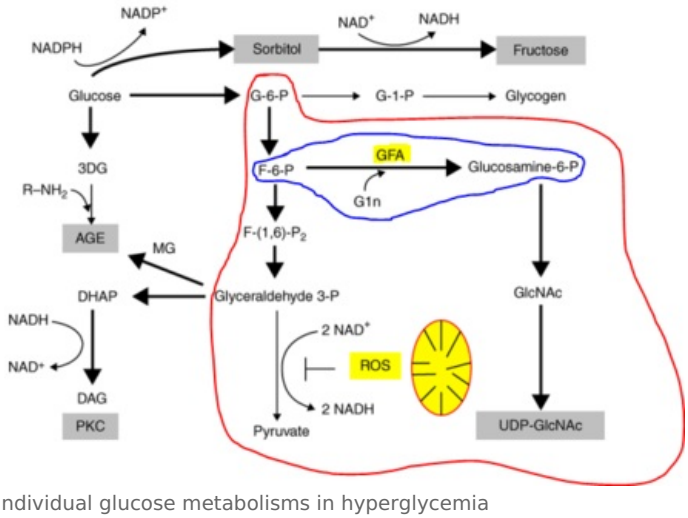
Superoxide activates nuclear poly-ADP-ribose polymerases (PARPs), which lead to the **accumulation of glycolysis metabolites**. It also activates the polyol, hexosamine and PKC pathways. This leads to an increase in **vascular complications**.

Hexosamine pathway

Inside the cells, glucose is converted to glucosamine-6-phosphate, which is further converted to **UDP-N-acetyl-glukosamine**. It binds to serine and threonine residues and modifies transcription factors. As a result, **pro-inflammatory and procoagulant factors** are overexpressed.

Protein kinase C pathway

The *dihydroxyacetone* formed during glycolysis is converted to *glycerol phosphate*, in fact to *diacylglycerol*, which activates protein kinase C. The action of PKC is manifested by **increased coagulation**, vasoconstriction and then vascular occlusion, which leads to **ischemia**. It also acts **pro-inflammatory** and **damages proteins and DNA**.



Individual glucose metabolisms in hyperglycemia

Ischemia

- Increased endothelin (**ET-1**) production, reduced formation of nitric oxide (**eNOS**) – vasoconstriction, hypertension.
- Increased production of plasminogen activator inhibitor (**PAI-1**) – reduction of fibrinolysis (increased hemocoagulation).
- Increased production of growth factor (**TGF-β**) – collagen and fibronectin production (vascular occlusion).

Inflammation and tissue damage

- Already mentioned **PAI-1**.
- Increased expression of necrotizing factor (**NF-κB**) – determines the production of cytokines and growth factors.

- Increased amount of **NADPH oxidases** – increase in ROS (oxidative tissue damage).

Increased production of angiogenetic **VEGF** (*vascular endothelial growth factor*) causes angiogenesis in some organs (for example retina – **retinopathy**).

The AGEs pathway

Advanced glycation end products (AGEs) are formed by the reaction of the carbonyl group of a reducing saccharide with the amino group of a protein. Then AGEs interact with RAGE, which triggers the production of cytokines and growth factors.

Molecular basis of organ changes in long-term hyperglycemia

Eye damage

Accumulation of sorbitol in the eye lens retains water, which reduces the transparency of the lens (lens clouding, cataract).

Deterioration in the conduction of excitations by neurons

The accumulation of sorbitol in Schwann cells and neurons disrupts axonal conduction (polyneuropathy). It mainly damages vegetative control, reflexes and sensation. The cells compensatory produce myoinositol against edema, which they then miss for other functions.

Weakening of the immune system

Cells that do not absorb enough glucose shrink due to extracellular hyperosmolarity. In lymphocytes, wrinkling reduces their function, such as superoxide production (important for immune defense responses).

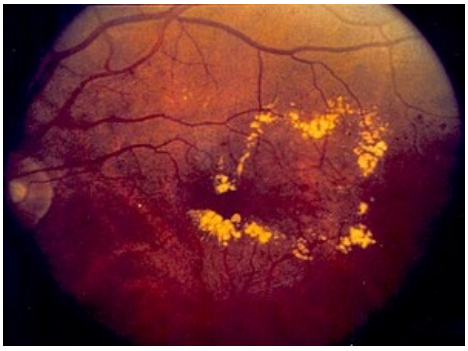
Patients with diabetes show an increased tendency to infections, such as skin (*furuncle*) or kidney (*polynephritis*). Then infections increase the need for insulin because they lead to a greater release of its antagonists.

Thromboembolic complications

Hyperglycemia promotes the production of carbohydrate-containing plasma proteins (fibrinogen, haptoglobin, α2-macroglobulin, coagulation factors V and VIII). In this way, clotting readiness, blood viscosity and thromboembolic risk may increase.

Diabetic angiopathy and its effect on organ systems

By binding glucose to the free amino groups of proteins and subsequent irreversible rearrangement, AGEs (*advanced glycation end products*) are formed, which are more common in old age. AGEs bind to cell membrane receptors and may thereby promote collagen deposition in the basement membranes of blood vessels. Connective tissue formation is partially stimulated by TGF, in addition collagen fibers can be altered by glycation. Both changes cause thickening of the basement membranes with reduced permeability and narrowing of the lumen (*microangiopathy*).



Macular edema based on diabetic retinopathy

Retinal disorder

As a result of microangiopathy, changes occur in the retina of the eye, which can eventually lead to blindness (**retinopathy**).

Kidney disorder

Renal**glomerulosclerosis** (*Kimmelstiel-Wilson syndrome*) develops, which can lead to proteinuria, decreased GF by glomerular death, hypertension, and renal insufficiency. Due to the high concentration of AMK in the plasma, hyperfiltration of still intact glomeruli occurs, thereby are also damaged.

Cardiovascular disorders

Hypertension promotes (in conjunction with an increase in VLDL in the blood and increased coagulation readiness) the development of **macroangiopathy**that can lead to further kidney damage, heart and cerebral infarction, and peripheral vascular occlusion.

Erythrocyte disorders

Glucose can react with hemoglobin HbA to HbA1c, the elevated blood levels of which indicate prolonged or repeated hyperglycaemia. HbA1c has a higher affinity for oxygen than HbA and therefore releases it less in the periphery. Persistent insulin deficiency leads to a decrease in 2,3-bisphosphoglycerate (BPG) in erythrocytes, which as an allosteric regulator of hemoglobin reduces its affinity for oxygen. BPG deficiency also results in increased HbA affinity for oxygen.

Disorders in pregnant women

In diabetic mothers, hypertrophic newborns are born to a greater extent, as a result of increased blood AMK levels, which could lead to greater somatropin (STH) secretion.

Late complications of diabetes include **diabetic macroangiopathy**, which is identical to atherosclerosis in non-diabetic patients, and **diabetic microangiopathy**.

Albuminuria

Urinary albumin excretion does not physiologically exceed 30 mg / 24 hours (i.e. 20 mg / min or about 15-20 mg / l)[1]. However, by standard tests for proteinuria (using diagnostic strips, sulfosalicylic acid test), protein can only be detected when the concentration of albumin exceeds about 150 mg / l, i.e. when it is practically 10 times higher[2]. Losses of smaller amounts of albumin (30-300 mg / 24 hours) are evident by immunochemical methods.

*In the older literature, the term **microalbuminuria** was used for small losses of albumin, which are demonstrable immunochemically but not by routine proteinuria tests.*

Screening for albuminuria is especially valuable in patients with type 2 diabetes mellitus, but also in other disorders of glucose metabolism and in hypertensive patients. The finding of small amounts of albumin in the urine is an early sign of complications of these diseases, especially diabetic or hypertensive nephropathy and vasculopathy, and is often a reason to intensify treatment.

An increase in albuminuria is a very sensitive indicator of glomerular damage. This is due to the fact that albumin crosses the glomerular membrane in small amounts even physiologically. However under normal circumstances, it is almost completely resorbed in the proximal tubules. However, the tubular resorption capacity of albumin is practically exhausted already during the physiological filtration of albumin; any increase in the concentration of this protein in the glomerular filtrate therefore leads to a rapid increase in the concentration of albumin in the definitive urine[2].

Albuminuria			
	mg/24 hours	**µg/min**	**mg/mmol creatinine**
standard	< 30	< 20	< 3,5
increased albuminuria	30–300	20–200	3,5–35
detectable proteinuria	> 300	> 200	> 35

Albuminuria needs to be quantified more accurately to monitor disease progression and manage treatment. Albumin is determined in **urine collected overnight** and losses are converted to µg albumin per minute. Values less than 100 µg/min usually correspond to reversible damage, which may be affected by careful compensation of diabetes and arterial hypertension[1].

Another option is to determine the albumin in the first morning urine sample and calculate the**albumin / creatinine ratio**. Physiologically, this index is around 2.8–22.8 g albumin per mole of creatinine[2].

In order for albuminuria to be meaningful, urinary tract infection should be ruled out.

Links

- ws:Mechanismus hyperglykémií indukovaného poškození tkání

Related articles

- Proteinuria
- Albuminuria

External links

- Mikroalbuminurie (česká wikipedie)
- Albuminuria (anglická wikipedie)

Source

-

References

1. ZIMA, Tomáš, et al. *Laboratorní diagnostika.* 2. edition. Prague : Galén a Karolinum, 2007. 906 pp. pp. 106-7, 121-2. ISBN 978-80-246-1423-6.
2. RACEK, Jaroslav, et al. *Klinická biochemie.* 2. edition. Prague : Galén, 2006. 329 pp. pp. 170. ISBN 80-7262-324-9.

}}

Kategorie:Patobiochemie Kategorie:Biochemie Kategorie:Vnitřní lékařství Kategorie:Nefrologie